III

A REVIEW OF THE SEROLOGICAL RESULTS OF THE TREATMENT OF SYPHILIS IN THE NOTTINGHAM CLINIC

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FOR many years after the introduction of salvarsan and its substitutes into the treatment of syphilis opinion as to the efficacy of these drugs was expressed chiefly in the form of impressions gained by individual observers without adequate statistical backing. Abroad, and especially in the United States, a vast literature of well-studied series has lately sprung up, based mainly on the alternating continuous system of treatment. In this country the simultaneous intermittent system is widely followed, but detailed reports have been few. A survey of the records of the Nottingham Clinic has, therefore, been attempted in order to gain a true estimate of what has been accomplished, using a simultaneous intermittent system of therapy.

The serological results only are considered in this review.

PART I.—STATISTICAL DATA (MALES)

The following rules were observed in selecting cases, and no case was chosen unless the first course had been strictly completed. Any irregularity after the first course is indicated by notes :—

(1) A course must consist of not less than 5·0 gm. of Ab.C., in conjunction with a minimum of 5 gr. Hg., or of 2·0 gm. Bi., over a period of not more than 4 months.

(2) To qualify for admission to the category of cases treated with two regular courses the patient must have received a first course, defined as above, commenced the second course within 3 months of the end of the first course, and completed it not more than 4 months later. Similarly with cases classified as having been treated with three or more courses.

(3) For the purpose of estimating the immediate effect

of a course of treatment the blood test must have been taken within 1 month of completion of the course.

The total number of cases of syphilis presenting themselves for the first time at the Nottingham Clinic between June, 1917, and the end of June, 1934, was 6,601 (4,072 men and 2,529 women). Of these 596 (412 men and 184 women) were eligible for this review.

Comparison of Different Brands of Arsenobenzene Compounds, as Judged by the Effect of One Course on the W.R.

Table A shows

(*a*) Comparison of the effects on the serum reactions in sero-positive primary syphilis (S.2), early secondary with roseola (S.3), and early secondary with lenticulo-papular eruptions (S.4) of different brands of Ab.C., in conjunction with approximately the same amounts of Hg.

(*b*) Similar comparison of effects of Hg. with those of Bi., in conjunction with approximately the same amounts of Ab.C.

(*c*) Comparison of the adjuvant effect of Hg. with that of Bi. in one course.

Table A

Brand of Ab.C.	Stage of syphilis.	Mercury (not less than 5 gr.).					Bismuth (not less than 2·0 gm.).				
		Number of cases.	++	+	±	−	Number of cases.	++	+	±	−
N.A.B.	S.2	15	—	—	1	14	39	—	1	1	37
	S.3	3	1	—	—	2	13		1	—	12
	S.4	6	—	—	—	6	12	—	1	—	11
	Totals	24	1	—	1	22	64	—	3	1	60
Novo-stab	S.2	—	—	—	—	—	52	2	—	—	50
	S.3	—	—	—	—	—	7	—	—	—	7
	S.4	—	—	—	—	—	19	1	—	1	17
	Totals	—	—	—	—	—	78	3	—	1	74
Totals	S.2	15	—	—	1	14	91	2	1	1	87
	S.3	3	1	—	—	2	20	—	1	—	19
	S.4	6	—	—	—	6	31	1	1	1	28
	Totals	24	1	—	1	22	142	3	3	2	134

Comparison of the Response to One and to Two Courses of Treatment in Different Stages of Syphilis

As Table A does not disclose any marked difference in the therapeutic effect of either Ab.C. used, or in the adjuvant effect of Bi. or Hg., the brand of Ab.C. and the adjuvant metal have been disregarded in studying the effects of treatment on the serum reactions in the different stages of infection.

The effects of the first course of treatment, as judged by the Wassermann reaction within a month of the termination of the course in

(A) Sero-negative primary cases ;
(B) Sero-positive primary cases ;
(C) Early secondary cases with roseola and/or lenticulo-papular eruptions, and perhaps mucous membrane lesions ;
(D) Cases with infections of more than 6 months' duration and with positive Wassermann reactions, or with active signs of disease, or both ;

are shown in Table B, and the effects of two regular courses in the same types of case are shown in Table C.

Table B.—*Effect of First Course of Treatment*

Stage as explained in text.	Number of cases.	Wassermann reactions within a month of end of course.			
		⧺	+	±	—
(A)	101	—	—	—	101
(B)	100	2	1	3	94
(C)	53	2	2	1	48
(D)	157	102	25	9	21

Table C.—*Effect of Two Courses of Treatment, the Second within Three Months of the First*

Stage as explained in text.	Number of cases.	Wassermann reactions within a month of end of course.			
		⧺	+	±	—
(A)	72	1	—	—	71
(B)	48	1	1	—	46
(C)	22	—	—	—	22
(D)	70	41	9	3	17

The Prognostic Import in Early Cases of Syphilis of the Serological Response to the First Two Courses of Treatment

In order to ascertain the prognostic import of the serological response to the first two courses of treatment, the later histories of the early cases shown in Tables B and C have been traced out.

Sero-negative Primary Cases whose Serum Reactions were Negative at the End of the First Course (101 *Cases*)

Of the 101 cases :

One (19261) defaulted after the first course, but reported intermittently during the following $2\frac{1}{2}$ years, receiving a further 3·75 gm. Ab.C. and 5·4 gm. Bi. W.R. + at end of first year of treatment. Otherwise repeatedly negative to 44 months from first visit.

One (C.544) gave W.R. + after a full second course. W.R. — after third and fourth courses. Rest. W.R. — repeatedly to 54 months from first visit.

One (6255) defaulted for 8 months. W.R. — on return. Received 3·75 gm. Ab.C. and defaulted. 26 months later W.R. +.

Of the remaining 98 cases, 87 attended later than the end of the first course. These can be divided into 61 who attended for further treatment regularly and 26 whose further attendance was irregular.

Of the regular attenders, 27 received 1 further course ; 26 received 2 further courses ; 7 received $2\frac{1}{2}$ further courses ; and 1 received 3 further courses.

Of the irregular attenders, 4 received half a further course ; 1 received 1 further course ; 10 received $1\frac{1}{2}$ further courses ; 2 received 2 further courses ; 3 received $2\frac{1}{2}$ further courses ; 6 received treatment too irregular in respect of drugs and intervals to be classified.

All of the 87 remained negative under treatment and observation lasting (counting from the last injection of the first course) from 3–6 months in 11 cases ; from 6–9 months in 9 cases ; from 9–12 months in 5 cases ; from 12–18 months in 13 cases ; from 18–24 months in 16 cases ; from 2–3 years in 19 cases ; from 3–4 years in 10 cases ; from 4–5 years in 3 cases ; from 5–6 years

in 1 case. The C.S.F. was not examined in any case.

Thus in the 101 cases of sero-negative primary syphilis shown in Table B there were 90 who attended later, and of these 3 relapsed after the first course.

Sero-negative Primary Cases shown in Table C (72 Cases)

Of the 72 cases :

All but 1 have been dealt with in the commentary on cases shown in Table B. The 1 case (6129) not included (because blood tests had not been carried out within a month of the completion of the course) had the following history : 2 full courses, followed by a year on Hg. pills * ; W.R. — at beginning of treatment, at end of second course and repeatedly to 22 months from last injection in first course.

Sero-positive Primary Cases whose W.R.'s were not Negative at the End of the First Course (6 Cases)

Of the 6 cases :

Three finished the first course with ⧺ or + W.R.'s.

No. 21661 with W.R. ⧺ at end of first course defaulted.

No. 21212 gave W.R. ⧺ at end of first, second and third full courses when he defaulted.

No. 13820 with W.R. + at end of first course attended irregularly to receive a further 3·15 gm. Ab.C. and 1·2 gm. Bi. when he defaulted. Eight months later W.R. ⧺, but no signs of active syphilis when he reported in answer to a letter.

Of the 3 cases who ended the first course with W.R. ± :—

No. 11818 received a further 2½ courses. W.R. — repeatedly to 38 months from end of first course.

No. E.254 received a further 3·45 gm. Ab.C. and Hg. pills. W.R. —. Defaulted 5 months. W.R. +. 4·35 gm. Ab.C. and pills. Defaulted 8 months. W.R. —. Rest. W.R. — to 52 months from + result.

No. 2176 received 1 further course when W.R. +. Defaulted.

* " Pills " refers to Pil. Hydrarg. gr. i or ii, t.i.d. " Hg. gr." refers to Squire's Cream.

Sero-Positive Primary Cases whose W.R.'s were Negative at the End of the First Course (94 *Cases*)

Of the 94 cases :

There were 8 in which later tests gave other than negative reactions. The further history is as follows :—

No. 18814.—Full course. W.R. —. Irregular full course. Defaulted 9 months. W.R. ±. 1·95 gm. Ab.C. and 0·8 gm. Bi. Defaulted 1 month. W.R. —. Defaulted.

No. 15405.—Full course. W.R. —. Full course. W.R. + (repeated). Full course. W.R. —. Rest. W.R. — to 26 months (*i.e.*, 14 months after second positive reaction).

No. 11616.—Defaulted. Reported in 16 months. W.R. +.

No. 12653.—Full course. W.R. —. Defaulted 10 months. W.R. +. 3·45 gm. Ab.C. and 3·6 gm. Bi. W.R. —. 2·0 gm. Bi. W.R. —. Rest. W.R. — to 77 months.

No. E.517.—Full course. W.R. —. Hg. pills 4 months. W.R. + (repeated). Full course. W.R. —. Full course. W.R. —. Pills 6 months. Rest. W.R. — to 45 months (*i.e.*, 32 months after last W.R. +).

No. E.62.—Defaulted 10 months. W.R. —. 5·1 gm. Ab.C. and pills. W.R. —. 3·75 gm. Ab.C. and pills. Defaulted 8 months. W.R. + (repeated). 4·35 gm. Ab.C. and pills. W.R. +. 2·8 gm. Bi. W.R. + (69 months from end of first course).

No. D.850.—3·0 gm. Ab.C. and Hg. gr. vii. W.R. —. 7·0 gm. Ab.C. and pills. W.R. +. 2·85 gm. Ab.C. and pills. Rest 6 months. W.R. +. 4·95 gm. Ab.C. and pills. W.R. +. 2·0 gm. Bi. W.R. —. 2·0 gm. Bi. W.R. — to 48 months (25 months from last + W.R.).

No. D.857.—Pills 4 months. W.R. +. 2·05 gm. Ab.C. and pills. W.R. +. 4·5 gm. Ab.C. and pills. W.R. +. 4·05 gm. Ab.C. and pills. W.R. —. 2·0 gm. Bi. and then pills. W.R. —. Rest 18 months. W.R. — to 60 months.

Of the remaining 86 cases, 74 attended later than the first course for treatment and observation, or for observation only. These may be divided into 49 who attended regularly throughout, and 25 whose further treatment was more or less irregular.

Of the 49 who attended regularly, 19 received 1 further course; 5 received 1½ further courses; 20 received 2 further courses; 3 received 2½ further courses; 2 received 3 further courses.

Of the 25 who attended irregularly, 11 received half a further course; 5 received 1 further course; 4 received 1½ further courses; 3 received 2 further courses; and 2 received no further treatment.

All of the 74 remained negative serologically under treatment and observation extending over the following periods after the first course: 3–6 months in 16 cases; 6–9 months in 5 cases; 9–12 months in 5 cases; 12–18 months in 8 cases; 18–24 months in 8 cases; 2–3 years in 15 cases; 3–4 years in 9 cases; 4–5 years in 5 cases; 5–6 years in 1 case; 7–8 years in 1 case; 10–11 years in 1 case. The C.S.F. was not examined in any case.

In Table D below the after-histories of the sero-positive primary cases, so far as they were traced above, have been summarised for ease of reading. All who attended regularly for at least 2 courses are entered under the side-heading " Further Treatment Regular."

Sero-Positive Primary Cases shown in Table C (22 Cases)

All of these were included in Table B, and their after-histories have been commented on above.

Early Secondary Cases whose W.R.'s were not Negative at the End of the First Course (5 *Cases*)

The further history of these 5 cases is as follows:—

Two did not attend later (22474 W.R. ± and D.954 W.R. +).

One (16444) with W.R. + received a second course. W.R. —. Hg. gr. ix and Bi. 2·0 gm. Rest. W.R. — repeatedly to 25 months.

One (15603) with W.R. + received 2·0 gm. Bi. W.R. ±. 4·65 gm. Ab.C. W.R. —. 2·4 gm. Bi. W.R. —. Full course. W.R. —. Rest. W.R. — to 27 months.

One (22206) with W.R. ± received 1·75 gm. Ab.C. and 1·0 gm. Bi. W.R. +. 3·0 gm. Ab.C. and 3·4 gm. Bi. W.R. — (*i.e.*, 8 months).

TABLE D.—*Comparison of the Behaviour under Further Treatment and Observation, or under Observation only, of Sero-Positive Primary Cases which ended the First Course with ⧺ or +, ± and — W.R.'s Respectively, Considered Separately according to the Regularity or otherwise of the Treatment after the First Course.*

Further treatment.	Reactions at end of first course.	Reactions subsequent to first course.				Observation for less than six months after suspension of treatment.
		Strongest during active further treatment.	At end of observation of not less than six months following suspension of treatment.			
1.	2.	3.	4.			5.
			Pos.	Doubt.	Neg.	
Regular.	⧺ or +	Pos. 1	—	—	—	1
		Doubt. —	—	—	—	—
		Neg. —	—	—	—	—
	±	Pos. 1	—	—	—	1
		Doubt. —	—	—	—	—
		Neg. 1	—	—	1	—
	—	Pos. 3	—	—	3	—
		Doubt. 1	—	—	—	1
		Neg. 49	—	—	28	21
Irregular.	⧺ or +	Pos. —	1*	—	—	—
		Doubt. —	—	—	—	—
		Neg. —	—	—	—	—
	±	Pos. 1†	—	—	1	—
		Doubt. —	—	—	—	—
		Neg. —	—	—	—	—
	—	Pos. 3	1	—	2	—
		Doubt. —	—	—	—	—
		Neg. 25	1‡	—	16	9

* Received no further test during active treatment, and is therefore not shown in Column 3.

† Subsequently received 4·35 gm. Ab.C. and pills. W.R. — during next 52 months.

‡ Refers to Case 11616, and therefore not shown in Column 3.

Early Secondary Cases whose W.R.'s were Negative at the End of the First Course (48 *Cases*)

In one of the 48 cases the later history showed other than negative reactions. No. 20870 received a further 4·2 gm. Ab.C. and 1·6 gm. Bi. W.R. —. Defaulted 2 months. W.R. ±. Defaulted.

Of the remaining 47 cases, 43 attended later than the first course for treatment and observation, or for observation only. These 43 may be divided into 24 which attended regularly for further treatment and 19 which attended irregularly.

Of the 24 regular attenders, 10 received 1 further course; 3 received 1½ further courses; 10 received 2 further courses; 1 received 2½ further courses.

Of the 19 irregular attenders, 2 received no further treatment; 7 received half a further course; 5 received 1 further course; 5 received 1½ further courses.

Of the 2 who received no further treatment, 1 reported 10 months later when the W.R. was negative and 1 reported 14 months later with a fresh infection (*Sp. pall.* present and W.R. +, reduced to negative in 1 course).

None of the irregular attenders who received 1½ further courses attended with such regularity as to enable them to be included with those who received at least 2 regular courses from the commencement.

All of the 43 cases remained negative under treatment and observation, or observation only, extending over the following periods: 3–6 months after the first course in 4 cases; 6–9 months in 7 cases; 9–12 months in 8 cases; 12–18 months in 3 cases; 18–24 months in 3 cases; 2–3 years in 5 cases; 3–4 years in 6 cases; 4–5 years in 5 cases; 6–7 years in 1 case; 10 years in 1 case.

The C.S.F. was not examined in any case.

In Table E the later results have been classified on the same lines as in Table D.

Early Secondary Cases shown in Table C (22 *Cases*)

The after-histories of all these cases have been included in the comments on cases recorded in Table B.

TABLE E.—*Comparison of the Behaviour under Further Treatment and Observation, on Observation only, of Early Secondary Cases which ended the First Course with ∔ or +, ± and — W.R.'s Respectively, considered separately according to the Regularity or otherwise of the Treatment after the First Course.*

Further treatment.	Reactions at end of first course.	Reactions subsequent to first course.				Observation for less than six months after suspension of treatment.
		Strongest during active further treatment.	At end of observation of not less than six months following suspension of treatment.			
			Pos.	Doubt.	Neg.	
1.	2.	3.	4.			5.
Regular.	∔ or +	Pos. —	—	—	—	—
		Doubt. —	—	—	—	—
		Neg. 1	—	—	1	—
	±	Pos. —	—	—	—	—
		Doubt. —	—	—	—	—
		Neg. —	—	—	—	—
	—	Pos. —	—	—	—	—
		Doubt. —	—	—	—	—
		Neg. 24	—	—	11	13
Nil or Irregular.	∔ or +	Pos. 1	—	—	—	1
		Doubt. 1	—	—	1	—
		Neg. —	—	—	—	—
	±	Pos. —	—	—	—	—
		Doubt. —	—	—	—	—
		Neg. —	—	—	—	—
	—	Pos. —	—	—	—	—
		Doubt. 1	—	—	—	1
		Neg. 19	—	—	14	5

TABLE F.—*Summary of the Results of the First Course of Treatment and of the After-histories of Sero-Negative Primary, Sero-Positive Primary and Early Secondary Cases shown in Table B.*

	Reaction at end of first course.	Number of cases.	Ceased to attend after first course.	Reactions. Strongest under continued treatment.			At the end of observation of not less than six months after suspension of treatment.			Observation for less than six months after suspension of treatment.
			1.	2.			3.			4.
				Pos.	Doubt.	Neg.	Pos.	Doubt.	Neg.	
Sero-negative primary.	∦ or +	—	—	—	—	—	—	—	—	—
	±	—	—	—	—	—	—	—	—	—
	Neg.	101	11	3*	—	87	—	—	67	23*
	Totals .	101	11	3	—	87	—	—	67	23
Sero-positive primary.	∦ or +	3	1	1	—	—	1†	—	—	1
	±	3	—	2	—	1	—	—	2	1
	Neg.	94	12	6	1	74	2‡	—	49	31
	Totals .	100	13	9	1	75	3	—	51	33
Early secondary.	∦ or +	4	1	1	1	1	—	—	2	1
	±	1	1	—	—	—	—	—	—	—
	Neg.	48	4	—	1	43	—	—	25	19
	Totals .	53	6	1	2	44	—	—	27	20

* Includes case No. 6255, for details of which see page 28. † Not shown in Column 2 as no tests taken during further active treatment.
‡ One case received no treatment after first course and is not shown in Column 2.

Note.—Sero-Positive Primary Cases, Column 2.—The 7 cases shown as having positive reactions "during continued treatment" include 3 who did so after default of 10, 10 and 16 months.

Statistical Data (Females)

The same rules were observed in selecting female cases as for males, with this exception that the minimum amount of Ab.C. allowed in a full course was lowered to 4·0 gm. The tables should be interpreted as explained in the section devoted to males.

Comparison of Different Brands of Arsenobenzene Compounds, and of the Adjuvant Effect of Hg. with that of Bi., as Judged by the Effect of One Course on the W.R.

Table A

Brand of Ab.C.	Stage of Syphilis.	Mercury (not less than 5 gr.).					Bismuth (not less than 2·0 gm.).				
		Number of cases.	∓	+	±	−	Number of cases.	∓	+	±	−
N.A.B.	S.2	8	—	—	1	7	11	—	—	—	11
	S.3	3	—	—	—	3	14	—	—	—	14
	S.4	16	2	—	1	13	18	1	—	1	16
	Totals	27	2	—	2	23	43	1	—	1	41
Novostab	S.2	—	—	—	—	—	7	—	—	—	7
	S.3	—	—	—	—	—	10	—	—	2	8
	S.4	—	—	—	—	—	7	1	—	—	6
	Totals	—	—	—	—	—	24	1	—	2	21
Totals	S.2	8	—	—	1	7	18	—	—	—	18
	S.3	3	—	—	—	3	24	—	—	2	22
	S.4	16	2	—	1	13	25	2	—	1	22
	Totals	27	2	—	2	23	67	2	—	3	62

Comparison of the Response to One and to Two Courses of Treatment in Different Stages of Syphilis

Table B.—*Effect of First Course of Treatment*

Stage as explained in text.	Number of cases.	Wassermann reactions within a month of end of course.			
		∓	+	±	−
(A)	7	—	—	—	7
(B)	22	—	—	—	22
(C)	65	2	—	4	59
(D)	90	51	12	8	19

TABLE C.—*Effect of Two Courses of Treatment, the Second within Three Months of the First*

Stage as explained in text.	Number of cases.	Wassermann reactions within a month of end of course.			
		⧺	+	±	—
(A)	2	—	—	—	2
(B)	8	—	—	—	8
(C)	28	—	—	1	27
(D)	42	21	4	3	14

THE PROGNOSTIC IMPORT IN EARLY CASES OF SYPHILIS OF THE SEROLOGICAL RESPONSE TO THE FIRST TWO COURSES OF TREATMENT

Sero-Negative Primary Cases whose Serum Reactions were Negative at the End of the First Course (7 Cases)

Of these 7 cases :

Five attended later than the first course.

No. 20928 received a further full course. W.R. —. 2·0 gm. Bi. W.R. —. Rest. W.R. — to 18 months from end of first course.

No. 17802 received a further full course. W.R. —. 1·15 gm. Ab.C. and 2·0 gm. Bi. W.R. —. Rest. W.R.— to 44 months.

No. 14050 attended irregularly, receiving a further 0·3 gm. Ab.C. and 0·8 gm. Bi. in the next 5 months. Defaulted 2 months. W.R. ⧺. 3·0 gm. Ab.C. and 2·2 gm. Bi. W.R.+ (*i.e.*, 14 months from first course). Defaulted.

No. 6187 received a further 2·55 gm. Ab.C. and pills. W.R. —. Pills for 9 months. W.R. —. Rest. W.R. — repeatedly to 45 months from first course when W.R. ±. 3·0 gm. Ab.C. W.R. —. Hg. pills for 5 months. W.R.—. Rest 3 weeks. W.R. ⧺. 1·0 gm. Bi. W.R. —. 2·0 gm. Bi. W.R. —. Rest. W.R. — to 10 years from first course.

E.966 received a further 5·7 gm. Ab.C. and pills. W.R. —. 2·3 gm. Ab.C. and pills. Defaulted 4 months. W.R. +. 1·96 gm. Ab.C. and pills irregularly in next 16 months. Confined, when W.R. ⧺. 0·4 gm. Ab.C. and 0·4 gm. Bi. Defaulted. W.R. — 20 and 24 months after confinement. Baby's W.R. — at 2 and 17 months.

Sero-Negative Primary Cases shown in Table C

Both cases are detailed above under Nos. 20928 and 17802.

Sero-Positive Primary Cases whose W.R.'s were Negative at the End of the First Course (22 *Cases*)

In 1 case later tests gave other than negative reactions.

No. 14539 received a further 2·0 gm. Bi. W.R. —. Pills for 40 months during which time the W.R. was repeatedly negative. Eight months later W.R. —. A further 6 months later W.R. +. Full course. W.R. —. 2·6 gm. Bi. W.R. —. Rest. W.R. — to 10 months from positive result.

Of the remaining 21 cases, 16 attended later than the first course for treatment and observation, or for observation only. These may be divided into 8 who attended regularly throughout, and 8 whose further treatment was more or less irregular. Of the 8 who attended regularly, 1 received 1 further course ; 3 received 1½ further courses ; 4 received 2 further courses. Of the 8 who attended irregularly, 2 received a further half course ; 1 received 2 further half courses ; 3 received 1 further course ; 1 received a further 2½ courses ; 1 received an unknown amount (see case No. 7865 below).

All of the 16 remained negative serologically under treatment and observation extending over the following periods after the first course : 6–9 months in 3 cases ; 12–18 months in 3 cases ; 18–24 months in 1 case ; 2–3 years in 2 cases ; 3–4 years in 3 cases ; 4–5 years in 1 case ; 9–10 years in 1 case ; 10–11 years in 2 cases.

Case No. 7865 defaulted after the first course. Eleven years later she reported for a test, stating she had received a few injections at various clinics after leaving Nottingham. The W.R. was negative.

Sero-Positive Primary Cases shown in Table C (8 *Cases*)

All these cases have been discussed under Table B. In no case were reactions other than negative obtained later.

In Table D below the after-histories of the sero-positive primary cases, so far as they were traced above, have been summarised.

TABLE D

Further treatment.	Reactions at end of first course.	Reactions subsequent to first course.				Observation for less than six months after suspension of treatment.
		Strongest during active further treatment.	At end of observation of not less than six months following suspension of treatment.			
1.	2.	3.	4.			5.
			Pos.	Doubt.	Neg.	
Regular.	⧺ or +	Pos. —	—	—	—	—
		Doubt. —	—	—	—	—
		Neg. —	—	—	—	—
	±	Pos. —	—	—	—	—
		Doubt. —	—	—	—	—
		Neg. —	—	—	—	—
	—	Pos. —	—	—	—	—
		Doubt. —	—	—	—	—
		Neg. 9	1*	—	6	2
Irregular.	⧺ or +	Pos. —	—	—	—	—
		Doubt. —	—	—	—	—
		Neg. —	—	—	—	—
	±	Pos. —	—	—	—	—
		Doubt. —	—	—	—	—
		Neg. —	—	—	—	—
	—	Pos. —	—	—	—	—
		Doubt. —	—	—	—	—
		Neg. 8	—	—	6	2

* Received further full course when W.R. —. Details given on page 38 under Case No. 14539.

Early Secondary Cases whose W.R.'s were not Negative at the End of the First Course (6 *Cases*)

Two did not attend later than the first course.
W.R. ⧺ at end of first course.

One (13464) received a further course. W.R. —. 2·0 gm. Bi. WR. —. Rest.
W.R. — to 6 years from first course.
One (171) attended irregularly and received a further 1·3 gm. Ab.C. and Hg. gr. iii. W.R. ⧺ 1 year after first course.

W.R. ± at end of first course.

One (22526) received a further course. W.R. — at 8 months. Defaulted.

One (20892) received 2·4 gm. Bi. W.R. —. 2·0 gm. Bi.

W.R. —. Rest. W.R. — to 22 months.

Early Secondary Cases which were Negative at the End of the First Course (59 *Cases*)

In 8 of the 59 cases the later histories showed other than negative reactions.

No. 20551 defaulted 10 months. W.R. ∔. Received 1·95 gm. Ab.C. and 3·0 gm. Bi. in 7 months. W.R. ±. Defaulted.

No. 15875 received a full course. W.R. —. Full course. W.R. —. Rest 4 months. W.R. ∔ (repeated). Full course. W.R. —. 2·4 gm. Bi. W.R. —. Rest. W.R. — to 47 months from relapse.

No. 14815 received 4·5 gm. Ab.C. and 0·8 gm. Bi. W.R. +. Hg. pills for 7 months. W.R. —. Rest. W.R. — to 57 months.

No. 6291 received 4·95 gm. Ab.C. and pills. W.R. —. Pills for 8 months. W.R. ∔. 0·9 gm. Ab.C. in next year. W.R. —. 3·0 gm. Ab.C. and pills. W.R. — to 71 months.

No. 6015 received 1·5 gm. Ab.C. and pills. Defaulted 4 months. W.R. ∔. 1·55 gm. Ab.C. and pills. Defaulted 8 months. W.R. +. 4·55 gm. Ab.C. and pills. W.R. — at 34 months. Defaulted.

No. D.400 received Hg. pills for 3 months. W.R. —. Hg. pills for 5 months. W.R. ±. 2·4 gm. Ab.C. and pills. Defaulted 21 months. W.R. — (*i.e.*, 38 months from first course).

No. D.788 received full course. W.R. ±. 3·75 gm. Ab.C. and pills. W.R. —. Pills for 4 months. W.R. ∔. 3·0 gm. Ab.C. and Hg. gr. iv. W.R. —. 2·3 gm. Ab.C. and pills. W.R. —. Pills. W.R. — to 53 months.

No. D.992 received a full course. W.R. —. Pills for 3 months. W.R. ∔. 2·55 gm. Ab.C. and Hg. gr. vi. W.R. —. 4·2 gm. Ab.C. and pills. W.R. —. Pills for 14 months. W.R. — repeatedly. Rest. W.R. — to 40 months.

Of the remaining 51 cases, 48 attended later than the first course for treatment or observation, or for observa-

tion only. These may be divided into 30 who attended regularly throughout, and 18 whose further treatment was more or less irregular.

Of the 30 who attended regularly, 12 received 1 further course; 12 received 1½ further courses; 6 received 2 further courses.

Of the 18 who attended irregularly, 10 received a further half course; 7 received 1 further course; 1 received 1½ further courses.

All of the 48 remained negative serologically under treatment and observation extending over the following periods after the first course: 3–6 months in 3 cases;

TABLE E

Further treatment.	Reactions at end of first course.	Reactions subsequent to first course.				Observation for less than six months after suspension of treatment.
		Strongest during active further treatment.	At end of observation of not less than six months following suspension of treatment.			
1.	2.	3.	4.			5.
			Pos.	Doubt.	Neg.	
Regular.	⧺ or +	Pos. — Doubt. — Neg. 1	—	—	—	—
			—	—	1	—
	±	Pos. — Doubt. — Neg. 1	—	—	—	—
			—	—	—	—
	—	Pos. 4 Doubt. — Neg. 30	—	—	4	—
			—	—	—	—
			—	—	25	5
Irregular.	⧺ or +	Pos. 1 Doubt. — Neg. —	—	—	—	1
			—	—	—	—
			—	—	—	—
	±	Pos. — Doubt. — Neg. 1	—	—	—	—
			—	—	—	2*
			—	—	1	—
	—	Pos. 3 Doubt. 1 Neg. 18	—	—	1	2
			—	—	1	—
			—	—	14	4

* Did not attend after first course, so not shown in Column 3.

TABLE F.—*Summary of the Results of the First Course of Treatment and of the After-histories of Sero-Negative Primary, Sero-Positive Primary and Early Secondary Cases shown in Table B.*

	Reaction at end of first course.	Number of cases.	Ceased to attend after first course.	Strongest under continued treatment.			At end of observation of not less than six months following suspension of treatment.			Observation for less than six months after suspension of treatment.
				Pos.	Doubt.	Neg.	Pos.	Doubt.	Neg.	
Sero-Negative Primary.	⋕ or +	—	—	—	—	—	—	—	—	—
	±	—	—	—	—	—	—	—	—	—
	−	7	2	3	—	2	—	—	4	1
	Totals .	7	2	3	—	2	—	—	4	1
Sero-Positive Primary.	⋕ or +	—	—	—	—	—	—	—	—	—
	±	—	—	—	—	—	—	—	—	—
	−	22	5	—	—	17	1*	—	12	4
	Totals .	22	5	—	—	17	1	—	12	4
Early Secondary.	⋕ or +	2	—	1	—	1	—	—	1	1
	±	4	2	—	—	2	—	—	1	1
	−	59	3	7	1	48	—	—	45	11
	Totals .	65	5	8	1	51	—	—	47	13

* Refers to Case No. 14539, for particulars of which see p. 38.

6–9 months in 3 cases; 9–12 months in 3 cases; 12–18 months in 3 cases; 18–24 months in 9 cases; 2–3 years in 8 cases; 3–4 years in 6 cases; 4–5 years in 6 cases; 5–6 years in 1 case; 7–8 years in 2 cases; 8–9 years in 1 case; 9–10 years in 2 cases; 12 years in 1 case. The C.S.F. was not examined in any case.

In Table E the later results have been classified on the same lines as in Table D, but referring to early secondary cases only.

Early Secondary Cases shown in Table C (28 Cases)

Of the 28 cases all ended the second course with negative reactions, except one which showed a ± reaction. The further history of this case has been traced previously (No. D.788).

Of the remaining 27 cases, all remained negative under treatment and observation except one, of which the history has been given (No. 15875). The history of the other cases has been given under Table B.

Part II.—Survey of Data in Combination with the Results obtained at St. Thomas's Hospital

A difficulty in any such review as this is to obtain a sufficient number of cases to permit reasonable inferences to be drawn. The Co-operative Clinical Group in the United States has overcome this by pooling statistics from five clinics. Thinking along these lines, it was decided to adopt Colonel Harrison's survey of the records from St. Thomas's Hospital [1] as a model, and the data already given follow closely his method of presentation. The Nottingham Clinic unit course (see Appendix) is similar to that used at St. Thomas's at the time of the survey; the rules for selecting cases laid down by Harrison were strictly adhered to in this review; the respective techniques for the Wassermann reaction give the same degree of sensitivity and specificity. It is therefore suggested that the combination of these two groups of figures will not distort their interpretation, but may demonstrate points which were hidden in the smaller numbers.

In Table A the figures were too small to allow inferences to be drawn. In the combined table below Table A has been combined with the St. Thomas's figures.

TABLE A.—*Combined*

Brand of Ab.C.	Stage of Syphilis.	MERCURY (not less than 5 gr.).					BISMUTH (not less than 2·0 gm.).				
		Number of cases.	++	+	±	−	Number of cases.	++	+	±	−
N.A.B.	S.2	43	2	—	3	38	39	—	1	1	37
	S.3	8	1	—	1	6	13	—	1	—	12
	S.4	62	10	4	7	41	12	—	1	—	11
	Totals	113	13	4	11	85	64	—	3	1	60
Novostab	S.2	3	—	—	—	3	57	2	—	1	54
	S.3	1	—	—	—	1	10	—	—	—	10
	S.4	5	—	—	1	4	29	1	1	3	24
	Totals	9	—	—	1	8	96	3	1	4	88
Totals	S.2	46	2	—	3	41	96	2	1	2	91
	S.3	9	1	—	1	7	23	—	1	—	22
	S.4	67	10	4	8	45	41	1	2	3	35
	Totals	122	13	4	12	93	160	3	4	5	148

Neither arsenobenzene compound can claim superiority, but the bismuth compares favourably with the mercury. After one course with Hg. as adjuvant, 23·8 per cent. of cases give other than negative reactions. The corresponding figure for Bi. is 7·5 per cent. This, of course, does not signify that Bi. as the adjuvant gives the better ultimate result. Stokes [2] found that within the first 3 months of treatment the percentage of patients securing Wassermann reversal is practically identical with both Bi. and Hg., whether used with "606" or "914," but with longer treatment (4–12 months) there appears to be a distinct advantage for Bi. over Hg. as adjuvant (39·8 per cent. reversals with neo-arsphenamine-bismuth *versus* 33·1 per cent. for neo-arsphenamine-mercury). Stokes further states that when the serology of patients treated with Bi., as compared to those treated with Hg., is examined in greater detail and over longer periods, the outcome is approximately the same under a scheme of alternating continuous therapy. Bi. may show a slight advantage when the intermittent system is followed.

The Wassermann reactions in various stages of syphilis

after one and two courses of treatment is seen in the combined tables below, which unite the St. Thomas's and Nottingham figures.

TABLE B.—*Combined*

Stage as explained in text.	Number of cases.	Wassermann reactions within a month of end of course.			
		++	+	±	−
(A)	216	1	2	3	210
(B)	220	7	1	14	198
(C)	220	22	13	26	159
(D)	695	485	65	41	104

TABLE C.—*Combined*

Stage as explained in text.	Number of cases.	Wassermann reactions within a month of end of course.			
		++	+	±	−
(A)	118	1	—	—	117
(B)	99	4	2	3	90
(C)	84	3	3	1	77
(D)	284	173	31	24	56

The sero-negative primary cases give the best results, as one would expect. Once the W.R. is positive the advantage of early treatment is not so obvious. Sero-positive primary cases (B) gave 10 per cent. reactions other than negative after the first course, and this figure had only fallen to 9 per cent. after the second course. Early secondary cases (C) gave for corresponding figures 27·7 and 8·3 per cent. The meaning of these figures can only be found by studying the later histories. The behaviour after the first course of the 220 sero-positive primary cases shown in Table B Combined has been tabulated below in Table D Combined.

For comparison Table E Combined shows the later histories of the 220 early secondary cases shown in Table B Combined.

During active treatment 16 W.R. results other than negative occurred among the sero-positive cases who attended regularly, including 8 from cases ending the first course with negative W.R.'s. The irregular attenders

TABLE D.—*Combined*

Further treatment.	Reactions at end of first course.	Reactions subsequent to first course.				Observation for less than six months after suspension of treatment.
		Strongest during active further treatment.	At end of observation of not less than six months following suspension of treatment.			
1.	2.	3.	4.			5.
			Pos.	Doubt.	Neg.	
Regular.	∔ or +	Pos. 3	—	—	—	3
		Doubt. —	—	—	—	—
		Neg. —	—	—	—	—
	±	Pos. 2	—	—	1	1
		Doubt. 3	—	—	2	1
		Neg. 1	—	—	1	—
	−	Pos. 5	—	—	3	2
		Doubt. 3	—	—	1	2
		Neg. 89	3	—	52	34
Nil or Irregular.	∔ or +	Pos. 2	1	—	1	1
		Doubt. —	—	—	—	—
		Neg. —	—	—	—	—
	±	Pos. 1	—	—	1	—
		Doubt. 1	—	—	1	—
		Neg. 3	—	—	3	1
	−	Pos. 6	1	—	4	1
		Doubt. 2	—	—	—	2
		Neg. 57	1	—	40	27

returned 12 W.R.'s other than negative, 8 of these again being in patients who ended the first course with negative W.R.'s.

The regular attenders among the early secondary cases returned during further active treatment 7 W.R. results other than negative, 3 of which followed a negative W.R. at the end of the first course. The irregular early secondary cases showed 16 W.R.'s other than negative, 5 of these being in patients who gave negative W.R.'s at the end of the first course.

The detailed account of these cases in Part I shows that 4 sero-positive cases with W.R.'s other than negative defaulted after the first course, compared with 14 similar

early secondary cases. This, no doubt, has favoured the later results of the early secondary cases.

TABLE E.—*Combined*

Further treatment.	Reactions at end of first course.	Reactions subsequent to first course.				Observation for less than six months after suspension of treatment.
		Strongest during active further treatment.	At end of observation of not less than six months following suspension of treatment.			
1.	2.	3.	4.			5.
			Pos.	Doubt.	Neg.	
Regular.	∓ or +	Pos. 4	—	—	2	2
		Doubt. —	—	—	—	—
		Neg. 13	2	—	9	2
	±	Pos. —	—	—	—	—
		Doubt. —	—	—	—	—
		Neg. 8	—	—	6	2
	—	Pos. 2	1	—	—	1
		Doubt. 1	—	—	1	—
		Neg. 55	1	—	33	21
Nil or Irregular.	∓ or +	Pos. 4	—	—	1	3
		Doubt. 2	—	—	1	1
		Neg. 4	—	—	1	3
	±	Pos. 3	—	—	—	3
		Doubt. 2	—	—	1	2
		Neg. 6	1	—	2	3
	—	Pos. 3	1	—	—	2
		Doubt. 2	—	—	1	2
		Neg. 60	1	—	38	26

After 6 months' observation, with approximately the same number of cases for both stages of infection, the sero-positive cases show 3 positive W.R.'s among the regular attenders and 3 among the irregular. The early secondary cases show 4 positive results among the regular attenders and 3 among the irregular. Again one cannot say what mass of latent syphilis lies hidden among the defaulters, but from this fairly large series of cases it seems fair to infer that the end results of treatment are approximately the same for sero-positive and early

secondary cases. Delay in commencement of treatment until the rash appears may allow the patient's own defence mechanism to develop and aid in the ultimate outcome. These results agree in their tendency with those obtained by Stokes,[3] who reports " satisfactory results " (combining figures for " cured with physical examination," " cured without physical examination " and " probation ") as follows :—

Sero-negative primary	. .	27·5 per cent.
Sero-positive primary	. .	23·2 ,,
Secondary (first year)	. .	18·4 ,,
Secondary (delayed)	. .	29·2 ,,

These figures were drawn up without regard to the treatment received, and should be regarded as indices and not as absolute figures representing " cure." Moore [4] found that " from two points of view, *i.e.*, the ultimate clinical outcome and the incidence of asymptomatic neurosyphilis, the results of treatment are slightly better in early secondary than in sero-positive primary syphilis."

Summary

In Table F Combined is summarised the after-history of sero-negative primary, sero-positive primary and early secondary cases shown in Table B Combined.

This table shows in a convenient form certain points, most of which have been mentioned already :—

(1) Satisfactory serological results after 6 months' observation following suspension of treatment were obtained in 99·3 per cent. of sero-negative primary cases, in 94·8 per cent. of sero-positive primary cases and in 93·2 per cent. of early secondary cases.

(2) The best serological results from the first course are obtained in the sero-negative primary stage.

(3) Sero-positive primary cases give better serological results after the first course than early secondary cases.

(4) Later treatment and observation show that in the final outcome sero-positive primary and early secondary cases have approximately the same prognosis.

(5) Some relapses to positive while under treatment in cases which ended the first course with negative results

TABLE F.—*Combined*

	Reaction at end of first course.	Number of cases.	Ceased to attend after first course.	Reactions.						Observation for less than six months after suspension of treatment.
				Strongest under continued treatment.			At end of observation of not less than six months following suspension of treatment.			
				Pos.	Doubt.	Neg.	Pos.	Doubt.	Neg.	
Sero-Negative Primary.	∔ or +	3	1	—	1	1	—	—	1	1
	±	3	1	—	1	1	—	—	1	1
	—	210	26	5	—	172	1	—	142	41
	Totals .	216	28	5	2	174	1	—	144	43
Sero-Positive Primary.	∔ or +	8	2	5	—	—	1	—	1	4
	±	14	2	3	4	4	—	—	9	3
	—	198	25	11	5	146	5	—	100	68
	Totals .	220	29	19	9	150	6	—	110	75
Early Secondary.	∔ or +	35	8	8	2	17	2	—	14	11
	±	26	6	3	2	14	1	—	9	10
	—	159	30	5	3	115	4	—	73	52
	Totals .	220	44	16	7	146	7	—	96	73

occur in all three stages under discussion. The cause of this is unknown.

Part III.—Survey of Statistical Data for Females

The number of female cases in this series is small, and the inferences suggested below may be modified by other investigators. Nevertheless, they may serve as a basis for further study. It should be remembered in comparisons with male cases that more As. is given in the unit course for the male.

Table A (females) shows 27 cases treated with one course of "914" and Hg., of which 4 gave W.R. results other than negative. The 67 cases treated with one course of "914" and Bi. gave 5 W.R. results other than negative. Bi. therefore gave better results than Hg. in this test.

Under Table B the sero-negative primary (A) and the early secondary (C) cases gave similar results to those obtained in male patients. The 22 female sero-positive primary cases all gave negative reactions against 94 per cent. out of 100 male cases. The later cases (D) favour the women. Of 157 men 86·6 per cent. gave other than negative W.R. results after the first course compared to 78·8 per cent. of 90 women.

Table C shows no difference between the sexes except under later cases (D), where women again react more favourably. After two courses 75·7 per cent. of 70 men gave W.R. results other than negative against 66·6 per cent. of 42 women.

Of the 7 sero-negative primary cases whose W.R.'s were negative at the end of the first course, 5 attended later, and of these 3 gave other than negative results in the further history. None of these 3 received full treatment, and 2 received Hg. pills after the first course. The prognostic import of a negative W.R. at the end of the first course cannot be judged from these cases.

Of the 22 sero-positive primary cases whose W.R.'s were negative at the end of the first course, 1 gave later tests other than negative, and in this case the later treatment had consisted of 2·0 gm. Bi. and Hg. pills.

Of the corresponding 94 sero-positive primary male cases 8 gave later tests other than negative, and of these

4 had received a full second course. The early prognosis for female sero-positive primary cases therefore seems better than for males.

Of 6 early secondary cases whose W.R.'s were not negative at the end of the first course 4 attended later. Disregarding the amount of further treatment, 3 had satisfactory later histories.

Of 5 corresponding male cases 3 attended later, and of these 2 had satisfactory further histories. No difference between the sexes is evident here.

Of 59 early secondary cases whose W.R.'s were negative at the end of the first course 8 gave later W.R. results other than negative. Of these, 1 case had received no treatment (defaulter) ; 4 cases relapsed after treatment with pills ; 1 case relapsed after an insufficient second course of " 914 " and Bi. ; 2 cases relapsed after further full courses of treatment. Of the 8 cases 6 finally gave satisfactory results (2 defaulted).

Of 48 corresponding men 1 relapsed after irregular treatment.

The early prognosis for early secondary cases seems slightly better in men.

Table F shows that whatever the chance of early serological relapse, the final results are similar in the sexes when treatment and observation are prolonged.

Of the primary and secondary female cases 1 gave a positive W.R. result after 6 months' observation following suspension of treatment. The corresponding male cases furnished 3 positive results, and, allowing for the difference in numbers, no difference in prognosis can be argued.

Summary

The results of treatment in females suggest that from the serological point of view

(1) Better results are obtained from one course of treatment with Bi. as the adjuvant drug than with Hg.

(2) Sex does not influence the results after one or two courses of treatment in the sero-negative primary and secondary stages.

(3) The sero-positive primary cases give slightly better results after the first course than the male, but this superiority is not apparent after the second course.

(4) On tracing the history of cases after the first course, whether full treatment has been received or not, the early serological outlook for sero-positive primary cases seems

slightly better in females, and for early secondary cases slightly better in males.

(5) The results for primary and secondary cases after treatment and observation for at least 6 months are similar for both sexes.

(6) Later stages react more favourably after one or two courses of treatment in female cases than in male.

Clinically it is well known that " syphilis is a milder disease in woman than in man." [5] Stokes [6] states that " the wife's response to treatment, even though pregnancy has never been a factor, is definitely better." In this series it is only in the late stages that it can be said that " syphilis deserves distinction on the score of chivalric ideals." [7]

I wish to thank Dr. J. C. Buckley for permission to use the material and for his interest and help in the work.

APPENDIX

The Unit Course

Day.	Nottingham Clinic.						St. Thomas's Hospital (1926).					
	Ab.C. gm.	and	Hg. gr.	or	Bi. gm.		Ab.C. gm.	and	Hg. gr.	or	Bi. gm.	
1	0·45		i		0·2		0·45		—		—	
8	0·45		i		0·2		0·45		i		0·4	
15	0·45		i		0·2		0·45		i		0·4	
22	—		i		0·2		—		—		—	
29	0·6		i		0·2		0·6		i		0·4	
36	0·6		i		0·2		0·6		i		0·4	
43	0·6		i		0·2		—		—		—	
50	—		i		0·2		0·75		i		0·4	
57	0·6		i		0·2		0·75		i		0·4	
64	0·6		i		0·2		—		—		—	
71	—		i		0·2		—		—		—	
78	0·6		i		0·2		0·75		i		0·4	
85	0·6		i		0·2		0·75		i		0·4	
92	—		—		—		0·75		i		0·4	
Average dose for women is 0·15 gm. Ab.C. less than shown above.							Pot. Iod. from 57th to 78th day.					

The method for the Wassermann test used by Harrison was No. 1 in the Medical Research Council Special Report, Series No. 14. The method used in Nottingham

is that of Fildes and Macintosh, Medical Research Council Special Report, Series No. 14, 1918.

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